Clinical Applications of Extracorporeal Blood Purification in Animals

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How pure is your Blood?
Contaminants in the blood can induce disease
✓ Endogenous toxins
✓ Exogenous poisons
✓ Administered drugs
✓ Viruses
✓ Bacteria
✓ Antibodies/proteins
✓ Abnormal cells
✓ Excessive water

Extracorporeal Blood Purification Therapy
**Extracorporeal Blood Purification Therapy**

**Hemodialysis:**
- Intermittent Hemodialysis
- Continuous Renal Replacement Therapy (CRRT)

**Hemoperfusion:**
- Charcoal
- Synthetic Sorbents

**Therapeutic Apheresis:**
- Therapeutic plasma exchange
- Cytapheresis

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**Hemodialysis: Indications in Renal Failure**

- Severe azotemia
- Severe oliguria or anuria
- Failure of conventional therapy
- Life-threatening fluid overload
- Life-threatening electrolyte or acid-base disorders
- Nephrotoxin removal
- Support for renal repair

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**Extracorporeal Blood Purification Retained Uremia Toxins**

<table>
<thead>
<tr>
<th>Urea</th>
<th>Guanidinoacetate</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO</td>
<td>Hippurate</td>
</tr>
<tr>
<td>Methylguanidine</td>
<td>myo-Inositol</td>
</tr>
<tr>
<td>Phenol</td>
<td>ADMA or SDMA</td>
</tr>
<tr>
<td>Phosphate</td>
<td>Dimethylarginine</td>
</tr>
<tr>
<td>p-Cresol</td>
<td>Spermine</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Pseudouridine</td>
</tr>
<tr>
<td>Hypoxanthine</td>
<td>Indoxyl sulfate</td>
</tr>
<tr>
<td>Spermidine</td>
<td>Phenylacetylglutamine</td>
</tr>
<tr>
<td>Xanthine</td>
<td>beta-Endorphin</td>
</tr>
<tr>
<td>Urate</td>
<td>Parathormone</td>
</tr>
<tr>
<td>Guanidinosuccinic acid</td>
<td>beta2-Microglobulin</td>
</tr>
<tr>
<td>Indole acetate</td>
<td>Water</td>
</tr>
</tbody>
</table>
Extracorporeal Blood Purification Therapy

Dialysis is the process by which solutes are transferred across a semipermeable membrane along diffusional gradients.

Extracorporeal Blood Purification (Hemodialysis)

Hemodialysis is a therapeutic process used to correct the fluid, acid-base, & electrolyte disorders and the toxicity associated with uremia. Solutes and water are transferred across an (artificial) membrane outside the patient’s body.

Extracorporeal Blood Purification (Hemodialysis)

Extracorporeal Circuit: Hemodialysis
- Vascular access
- Hemocompatible tubing
- Blood pump to regulate extracorporeal blood flow
- High-flux dialyzer for greatest permeability
- A source of anticoagulant
- Dialysate of appropriate composition to promote diffusion
**Extracorporeal Blood Purification**

**Uremia Toxins**

**Governing Principles:**
- Molecular size
- Degree & avidity of protein binding
- Distribution volume
- Lipid solubility
- Concentration gradient
- Diffusivity of solute
- Permeability of membrane
- Surface area of membrane

**Extracorporeal Blood Purification**

Blood → Dialysate

+100 mmHg → -200 mmHg

**Convection**

**Adsorption**

**Diffusion**

**Extracorporeal Blood Purification**

Blood → Dialysate

+100 mmHg → -200 mmHg

**Convection**

**Adsorption**

**Diffusion**

**Extracorporeal Blood Purification**

Blood → Dialysate

+100 mmHg → -200 mmHg

**Convection**

**Adsorption**

**Diffusion**
First “Artifical Kidney” (vividiffusion)
John Jacob Abel (1913)

Hemodialysis: Indications in Renal Failure

Vascular Access for Extracorporeal Therapies
Veterinary Hemodialysis: Indications in Renal Failure

**GOALS**—Correct the alterations in body fluid volume and composition including:

- Removal of endogenous uremia toxins
- Correction of dysregulated electrolytes
- Correction of depleted solutes
- Normalization of acid-base balance
- Correction of excess or deficit fluid volume
- Removal of exogenous toxins
- Normalization of altered systemic physiology
Patient Clearance (Kd•t):
✓ Solute removal over session

Hemodialysis: Removal of Endogenous Uremia Solutes

Hemodialysis: Removal of Endogenous Uremia Solutes

Hemodialysis: Removal of Endogenous Uremia Solutes

Hemodialysis: Removal of Endogenous Uremia Solutes

BUN(%) URR
pre
post
×

100BUN
pre
postBUN

URR(%) = postBUN - preBUN
preBUN × 100
Hemodialysis: Removal of Endogenous Uremia Solutes

Factors Influencing Removal of Uremia Toxins:
- Changes in Qb or Qd
- Clotting, ↓ surface area
- Access recirculation
- Inaccurate assessments of Qb
- Periods of bypass
- Imprecise assessments of Kd

Hemodialysis: Applications in Acute Kidney Injury

Hemodialysis: Applications for Severe Electrolyte Abnormalities

Within minutes of starting dialysis
- Increased HR
- Improvement in cardiotoxicity
- Reappearance of p-waves
- Short-term and long-term management
Hemodialysis (Ultrafiltration): Application for Overhydration

Dr. Thierry Francey (2003)

n=115

Proportion of Dogs (%)

Hydration (% BW)

Before Ultrafiltration

8 Liters Later

Hemodialysis (Ultrafiltration): Application for Overhydration

Before Ultrafiltration

24 Hours Later
Hemodialysis: Indications for Exogenous Toxin Removal

Acute Intoxications
- Delay in medical Rx
- Overt sign of toxicity
- Progressive clinical deterioration (esp. CNS)
- Limited endogenous clearance/metabolism
- Impairment of normal clearance routes
- Extracorporeal clearance faster than metabolism
- No specific antidote

Hemodialysis: Indications for Exogenous Toxin Removal

Indications:
- Removal of small MW, non protein bound solutes
- Ethylene glycol, caffeine,

Governing Principles:
- Molecular size
- Degree & avidity of protein binding
- Distribution volume
- Lipid solubility

Hemodialysis: Indications for Exogenous Toxin Removal

\[ V_d = 0.03 \, \text{L/kg} \]
Hemodialysis: Applications in Acute Intoxications

C Rollings et al, ACVIM Proc, 2004

Extracorporeal Blood Purification Therapy

Hemodialysis:
✓ Intermittent Hemodialysis
✓ Continuous Renal Replacement Therapy (CRRT)

Hemoperfusion:
✓ Charcoal
✓ Synthetic Sorbents

Therapeutic Apheresis:
✓ Therapeutic plasma exchange
✓ Cytapheresis

Extracorporeal Blood Purification Non Diffusible Solutes

Governing Principles:
✓ High molecular weight solutes
✓ Protein-bound solutes
✓ Lipid-bound solutes
✓ Cellular elements of blood
...are not amenable to dialytic removal and require alternative therapeutic strategies
Extracorporeal Blood Purification (Hemoperfusion)

Sorbent Materials
- Activated Charcoal
- Macroporous polymers
- Anion exchange resins

Sorbent Properties
- Large surface area
- Hyper-crosslinked
- Macroporous size
- Selective surface
- Hemocompatible
- Biocompatible

Activated Charcoal
- Most commonly used sorbent
- Internal surface area: 100 M^2/gm
- Pore size: 10 Å to 100,000 Å
- Microencapsulated for hemocompatibility
Extracorporeal Blood Purification (Hemoperfusion & Hemodialysis)

Sorbent Hemoperfusion/Hemodialysis

Indications:
- Broad spectrum of toxin removal
- High molecular weight & protein bound toxins
- Lipid soluble
- Unknown solute characteristics

Treatment Goals:
- 100% elimination of toxins and toxic metabolites
- Prevention of rebound

Extracorporeal Blood Purification (Hemoperfusion & Hemodialysis)

Indications for Hemoperfusion
- Acute toxin removal (lethal or severe)
- Drug overdose
- Poisoning
- Impairment of normal drug or solute excretion-hepatic, cardiac, or renal failure
- Toxins with molecular wt >500 D and <40,000 D
- Toxins that are significantly protein bound
**Extracorporeal Blood Purification**

**Hemoperfusion & Hemodialysis**

**Solute Removed with Hemoperfusion**

- **Barbiturates:**
  - Nonbarbiturate: hypnotics, sedatives & tranquilizers, promazine chlorpromazine

- **Analgesics:**
  - acetaminophen, salicylic acid, phenylbutazone, *Cox 1 & 2 NSAIDs*

- **Antimicrobials:**
  - gentamicin, isoniazid, chloramphenicol

- **Anticancer:** doxorubicin, cytoxan

- **Plant & Animal Toxins:** amanitin, diquat, paraquat

- **Cardiovascular:** digoxin, diltiazem, procainamide

- **Miscellaneous:** caffeine, cimetidine, phenols

- **Solvents:** carbon tetrachloride, ethylene oxide, ethylene glycol

- **Endogenous Toxins:** middle molecules, cytokines, bilirubin

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**Hemodialysis/Hemoperfusion for Acute Caffeine Intoxication**

**Kefr M 31 90**

**Human Lethal Concentration**

**Human Toxic Concentration**

<table>
<thead>
<tr>
<th>Human Lethal Concentration</th>
<th>Human Toxic Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 ppm</td>
<td>80 ppm</td>
</tr>
<tr>
<td>80 ppm</td>
<td>60 ppm</td>
</tr>
<tr>
<td>60 ppm</td>
<td>40 ppm</td>
</tr>
<tr>
<td>40 ppm</td>
<td>20 ppm</td>
</tr>
<tr>
<td>20 ppm</td>
<td>0 ppm</td>
</tr>
</tbody>
</table>

**Hemodialysis/Hemoperfusion Time (min)**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Serum Caffeine (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100 ppm</td>
</tr>
<tr>
<td>30</td>
<td>80 ppm</td>
</tr>
<tr>
<td>60</td>
<td>60 ppm</td>
</tr>
<tr>
<td>90</td>
<td>40 ppm</td>
</tr>
<tr>
<td>120</td>
<td>20 ppm</td>
</tr>
<tr>
<td>150</td>
<td>0 ppm</td>
</tr>
</tbody>
</table>

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**Hemodialysis/Hemoperfusion for Acute Enrofloxacin Intoxication**

**ERF / CPF (µg/ml)**

- **t1/2 = 2.9 h**
- **t1/2 = 29.8 h**
- **Cin = 26.2 µg/ml**
- **VD = 6.7 L (95% of BW)**

**Francy et al, et al, 2004**

<table>
<thead>
<tr>
<th>Time post injection (h)</th>
<th>ERF / CPF (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10 µg/ml</td>
</tr>
<tr>
<td>10</td>
<td>1 µg/ml</td>
</tr>
<tr>
<td>20</td>
<td>0.1 µg/ml</td>
</tr>
<tr>
<td>30</td>
<td>0.01 µg/ml</td>
</tr>
<tr>
<td>40</td>
<td>0.001 µg/ml</td>
</tr>
<tr>
<td>50</td>
<td>0.0001 µg/ml</td>
</tr>
<tr>
<td>60</td>
<td>0.00001 µg/ml</td>
</tr>
</tbody>
</table>

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**ERF**

**CPF**

**ER = 62%**

**FC = 49%**

**ER = 93%**

**FC = 73%**

**ER = 81%**

**FC = 64%**

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**Francey et al, et al, 2004**
Hemodialysis/Hemoperfusion for Acute Pentobarbital Intoxication

Pre Hemoperfusion
Post HP, Pre HD
Post Hemodialyzer

(75.4%)

Fischer, Pantaleo, et al, 2004

Extracorporeal Blood Purification
Acute Phenobarbital Intoxication

Extracorporeal Blood Purification
Toxin Rebound
**Hemodialysis/Hemoperfusion for Endogenous Toxins**

- Hyperbilirubinemia
- Endogenous Intoxications
- Ammonia
- Hepatotoxins
- Endotoxins
- Cytokines & inflammatory mediators
- Viruses and bacteria

**Hemodialysis/Hemoperfusion**

- for Endogenous Toxins

**Therapeutic Plasma Exchange**

- Contaminants in the blood can induce disease
  - Endogenous toxins
  - Exogenous poisons
  - Administered drugs
  - Antibodies/proteins
  - Abnormal cells

**Extracorporeal Blood Purification Therapy**

- Therapeutic Apheresis:
  - Therapeutic plasma exchange
  - Cytapheresis
Extracorporeal Blood Purification (Apheresis)

Therapeutic Plasma Exchange:
- Immune-mediated diseases
- Gammopathies
- Large toxic molecules
- Protein-bound toxins
- Dys-lipidemia

Cytapheresis:
- Plateletpheresis
- Leukapheresis
- Mononuclear cell (ie stem cell) collection
- Red cell exchange

Therapeutic Apheresis

Therapeutic Plasma Exchange
Centrifugal Apheresis: CaridianBCT Optia®
Extracorporeal Blood Purification (Apheresis)

Centrifugal Apheresis: CaridianBCT Optia®
Therapeutic Plasma Exchange (Filtration Plasmapheresis)

Selected Indications for Therapeutic Plasma Exchange in Human Medicine

Neuromuscular Diseases:
- Guillain-Barré syndrome
- Chronic inflammatory demyelinating polyneuropathy
- Myasthenia gravis
- Polymyositis (IgG/IgA/IgM)
- Lambert-Eaton myasthenic syndrome
- Idiopathic inflammatory demyelinating disease
- Polymyositis or dermatomyositis
- Paraneoplastic neurologic syndrome
- Stiff-person syndrome

Hematologic Diseases:
- Post transfusion purpura
- Thrombotic thrombocytopenic purpura
- ABO-incompatible marrow transplant
- Cryoglobulinemia
- Hyperviscosity syndrome
- Immune-mediated hemolytic anemia

Renal Diseases:
- Anti-gluomerular basement membrane antibody disease
- Rapidly progressive glomerulonephritis
- Hemolytic urinemic syndrome

Metabolic Disorders:
- Acute hepatic failure
- Poisoning, drug overdose

Potential Veterinary Indications for Therapeutic Plasma Exchange

<table>
<thead>
<tr>
<th>Condition</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myasthenia gravis</td>
<td>Immune-mediated hemolytic anemia</td>
</tr>
<tr>
<td>Systemic lupus</td>
<td>Immune-mediated thrombocytopenia</td>
</tr>
<tr>
<td>Lyme-associated nephritis</td>
<td>Immune-mediated polyarthritis</td>
</tr>
<tr>
<td>Pemphigus foliaceus</td>
<td>Acute polymyositis</td>
</tr>
<tr>
<td>Polycythemia</td>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Leukemia</td>
<td>Acute hepatic failure</td>
</tr>
<tr>
<td>Hyperviscosity syndrome</td>
<td>Drug overdose</td>
</tr>
<tr>
<td>Pure red cell aplasia</td>
<td>Exogenous toxin removal (i.e., amanita)</td>
</tr>
</tbody>
</table>
Neuromuscular disease
- Antibody-mediated inactivation of NM endplate
- Focal or generalized

Clinical consequences
- Megaesophagus
- Aspiration pneumonia
- Exercise induced weakness/collapse
- Respiratory failure

Therapeutic Plasma Exchange
Acquired Myasthenia Gravis

Conventional Management of Acquired Myasthenia Gravis

Anticholinesterase
- Pyridostigmine

Management of megaesophagus
- Elevated feeding
- Gastrointestinal protectants
- Aspiration pneumonia

Surgical excision of thymoma

Immunosuppression

Marley: myasthenia gravis

Signalment:
- 8 yr; MC; Bernese, 37.5 kg

History:
- June-July 2009—gagging, mediastinal mass identified and removed
- July-Aug 2009—Developed progressive weakness collapsing on walk, legs shaking, unable to raise head, megaesophagus, and pneumonia
- Sept. 17, 2009—Presented for therapeutic plasma exchange
- Recumbent, weak, non ambulatory, muscle atrophy
Marley: Treatment Summary

<table>
<thead>
<tr>
<th>Treatment Parameters</th>
<th>Rx 1 (Day 0)</th>
<th>Rx 2 (Day 1)</th>
<th>Rx 3 (Day 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Time (min)</td>
<td>158</td>
<td>191</td>
<td>228</td>
</tr>
<tr>
<td>Inlet Vol Process (ml)</td>
<td>4312</td>
<td>4302</td>
<td>4163</td>
</tr>
<tr>
<td>Plasma Removed (ml)</td>
<td>1728</td>
<td>1624</td>
<td>1928</td>
</tr>
<tr>
<td>Replacement Fluid (ml)</td>
<td>1599</td>
<td>1447</td>
<td>1795</td>
</tr>
<tr>
<td>Plasma Volumes Exchanged</td>
<td>1.0</td>
<td>1.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Removed ACh Antibody Titer (nmol/L)</td>
<td>3.57</td>
<td>0.21</td>
<td>0.65</td>
</tr>
<tr>
<td>ACh Antibody Removed (nmol)</td>
<td>6.17</td>
<td>0.43</td>
<td>1.25</td>
</tr>
</tbody>
</table>

Single Treatment Change in ACh Receptor Ab Titer to TPE

Marley: AChR Antibody Titers

<table>
<thead>
<tr>
<th>Date</th>
<th>AChR Titer* (nmol/L)</th>
<th>Clinical Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>23 Aug</td>
<td>3.05</td>
<td>Vomiting, weak, aspiration pneumonia</td>
</tr>
<tr>
<td>17 Sept</td>
<td>2.77</td>
<td>Weak, non ambulatory, vomiting</td>
</tr>
<tr>
<td>05 Oct</td>
<td>4.05</td>
<td>Clinically normal, rare vomiting, efts without elevation, normal ambulation and strength, Tapering medications.</td>
</tr>
<tr>
<td>13 Oct</td>
<td>5.08</td>
<td></td>
</tr>
<tr>
<td>19 Oct</td>
<td>3.76</td>
<td>Feb, 2009 — Off all medications</td>
</tr>
</tbody>
</table>

*Titers greater than 0.6 nmol/l are considered significant and positive for acquired myasthenia gravis.
**Marley: Day 1 (1st TPE Rx)**

Clinical Observations:
- Brighter attitude
- More engaged in treatment room
- Responsive to owner visit
- Stood with improved strength at end of treatment

**Marley: Day 2 (2nd TPE Rx)**

**Clinical Observations:**
- Walked from wards to treatment room
- Sternal posture during entire treatment
- Clinically normal strength, ambulation, mentation at end of treatment
- Pulled us back to the ward

**Marley: Day 5 (3rd TPE Rx)**

Clinical Observations:
- Walked from wards to treatment room
- Sternal posture during entire treatment
- Clinically normal strength, ambulation, mentation at end of treatment
- Pulled us back to the ward
Extracorporeal Blood Purification (Apheresis)

Marley: myasthenia gravis

08 September, 2009

07 October, 2009

Application of Therapeutic Plasma Exchange

Acquired Myasthenia Gravis

Day 0

Day 5

Ambulatory

Apparent resolution of regurgitation

Recurrence of aspiration pneumonia

Discharge from hospital

Apparent clinical remission

Radiographic resolution of megaesophagus

Ambulatory

Recall radiographs not taken

Time (days)

0 5 10 15 20

Dog 3

Dog 2

Dog 1

Discharge from hospital

Apparent clinical remission

Radiographic resolution of megaesophagus

Apparent resolution of regurgitation

Ambulatory
Application of Therapeutic Plasma Exchange
Immune-mediated Hemolytic Anemia

IMHA
- Antibody-mediated destruction of RBCs
- Intravascular or extravascular

Clinical consequences
- Lethargy, depression, anorexia
- Weakness
- Collapse
- Respiratory distress

Conventional Management of Immune-mediated Hemolytic Anemia

Supportive care
Immunosuppression:
- Glucocorticoids
- Cytotoxic agents
- Cyclosporin A
- Intravenous gamma globulin

Blood transfusion

Heathrow: Immune-mediated Hemolytic Anemia

12 July—Presented to rDVM for lethargy and inappetence
- PCV = 24%, TS 7.2, severe autoagglutination, WBC 9.39, T bili = 0.9 mg/dl
- Heartworm, Lyme, Ehrlichia, Anaplasma phagocytophila, RMSF negative

13 July—PCV = 18%, TS 8, WBC 15.1, 56,000 reticulocytes

14 July—doing well, stable, PCV 19%, TS 8.0 g/dl, icteric plasma

15 July—stable but PCV 18, TS 6.8 g/dl
Heathrow: Immune-mediated Hemolytic Anemia

12 July:
✓ Dexamethasone 9 mg IV once
✓ Cyclosporine 150 mg PO BID, then increased to 300 mg PO BID

13 July:
✓ Added prednisone 40 mg PO BID
✓ Added leflunamide 120 mg PO SID
✓ Famotidine 20 mg PO BID
✓ Doxycycline 200 mg PO BID
✓ Aspirin 81 mg PO SID

Heathrow: Treatment Summary

<table>
<thead>
<tr>
<th>Treatment Parameters</th>
<th>HCT</th>
<th>Rx</th>
<th>Vol Ex</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 July</td>
<td>12.5%</td>
<td>#1</td>
<td>1.2 (50%)</td>
</tr>
<tr>
<td>16 July</td>
<td>24.6%</td>
<td>#2</td>
<td>1.4 (50%)</td>
</tr>
<tr>
<td>17 July</td>
<td>29.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 July</td>
<td>28.4%</td>
<td>#3</td>
<td>1.1 (40%)</td>
</tr>
<tr>
<td>22 July</td>
<td>34.0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Therapeutic Plasma Exchange (IMHA)

Saline Slide Agglutination Test

Pre Treatment #1

Post Treatment #1
**Therapeutic Plasma Exchange (IMHA)**

Saline Slide Agglutination Test

<table>
<thead>
<tr>
<th></th>
<th>Pre-Treatment #2</th>
<th>Post-Treatment #2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Therapeutic Plasma Exchange (IMHA)**

Saline Slide Agglutination Test

<table>
<thead>
<tr>
<th></th>
<th>Post-Treatment #3</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Blood Cross Match**

<table>
<thead>
<tr>
<th></th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>Pre-Treatment 3</th>
<th>Post-Treatment 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor #1</td>
<td>3+</td>
<td>3+</td>
<td>2+</td>
<td>1+</td>
</tr>
<tr>
<td>Donor #2</td>
<td>3+</td>
<td>3+</td>
<td>2+</td>
<td>2+</td>
</tr>
<tr>
<td>Donor #3</td>
<td>4+</td>
<td>3+</td>
<td>2+</td>
<td>+/-</td>
</tr>
<tr>
<td>Auto</td>
<td>4+</td>
<td>3+</td>
<td>2+</td>
<td>1+</td>
</tr>
</tbody>
</table>
Therapeutic Plasma Exchange (IMHA)

Therapeutic Plasma Exchange (Polyneuritis Equi)

Therapeutic Plasma Exchange in a Horse
Effects of Apheresis on Serum Creatinine in a Dog with Lyme-Associated Nephritis

Effects of Apheresis on Proteinuria in a Dog with Lyme-Associated Nephritis

Conclusions:
- Technically complex and demanding therapies
- Narrowly targeted veterinary indications
- Therapeutic options for many diseases for which there is no effective or alternative therapy
- There is an increasing awareness and demand for these services throughout the world